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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/869,275	06/04/1997	CARL T. WITWER	T8616.CIPS	5556

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[REDACTED] EXAMINER

MARSCHEL, ARDIN H

[REDACTED] ART UNIT      [REDACTED] PAPER NUMBER

1631

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*LJ*

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>08/869,275</b>	Applicant(s) <b>Wittwer et al.</b>
	Examiner <b>Ardin Marschel</b>	Art Unit <b>1631</b>
		
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
<b>Period for Reply</b>		
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
<ul style="list-style-type: none"> <li>- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</li> <li>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</li> <li>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</li> <li>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</li> <li>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</li> </ul>		
<b>Status</b>		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Jul 2, 2002</u>		
2a) <input type="checkbox"/> This action is FINAL.      2b) <input checked="" type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.		
<b>Disposition of Claims</b>		
4) <input checked="" type="checkbox"/> Claim(s) <u>13-35, 55-59, 79-82, 87-92, and 118-172</u> is/are pending in the application.		
<del>4a) Of the above, Claim(s) 1-12, 36-54, 60-78, 83-86, and 93-117 have been</del> <sup><i>canceled</i></sup> <del>is/are withdrawn from consideration.</del>		
5) <input type="checkbox"/> Claim(s) _____ is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>13-35, 55-59, 79-82, 87-92, 118-160, and 163-170</u> is/are rejected.		
7) <input checked="" type="checkbox"/> Claim(s) <u>161, 162, 171, and 172</u> is/are objected to.		
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.		
<b>Application Papers</b>		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input checked="" type="checkbox"/> The proposed drawing correction filed on <u>Feb 9, 2001</u> is: a) <input checked="" type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
<b>Priority under 35 U.S.C. §§ 119 and 120</b>		
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of: 1. <input type="checkbox"/> Certified copies of the priority documents have been received. 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). *See the attached detailed Office action for a list of the certified copies not received.		
14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input checked="" type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
<b>Attachment(s)</b>		
1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		
6) <input type="checkbox"/> Other: _____		

Applicants' arguments, filed 7/2/02, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title includes both systems and methods whereas only systems are presently being claimed.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 13-18, 20, 23-32, 118, 128-130, 132, 135-144, 156-158, and 168 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Higuchi et al. [Bio/Technology 10:413(1992); already of record], taken in view of Haff et al. [Biotechniques, 10(1):102-112(1991)].

Higuchi et al. has been previously described of record as monitoring real time fluorescence in a PCR amplification method. The instant claims have been amended to include specific rates of temperature change during this process which are not specifically disclosed in Higuchi et al. Higuchi et al., however, performs PCR while utilizing a Perkin Elmer thermocycler model 480 as described on page 416, second column, in the section entitled "Continuous fluorescence monitoring of PCR.

Haff et al. describes automation of PCR amplification and compares the models 480 and 9600 with noting that the model 9600 is an improved, faster, version of thermocycler in the section bridging pages 110 and 111 entitled "Amplification Equivalency at Low Copy Number". On page 111, first column, lines 1-14, the 9600 is described as taking 60% less time for amplification but yet resulting in equivalent specificity. Thus, someone of ordinary skill in the art would be motivated to substitute the model 9600 for model 480 to get equivalent results but in less amplification time. The newly added instant limitations to claim 13, for example, requires heating and cooling at a rate of at

least 0.5 degrees C. per second. It is noted that the tubes used in the 9600 system also have thin walls for faster heat conduction as described on page 106, first column, third full paragraph. On page 107, Figure 3, a rate of temperature change is shown as a increase from below 69 degrees C. to 96 degrees C. in close to 35 seconds. This is a rate of temperature change of  $(96-69 \text{ degrees C.})/35 \text{ sec.} = 0.77 \text{ degrees C. per second}$ . This suggests that the tubes, heat transfer rate, etc. all supply a means of temperature change of over 0.5 degrees C. per second. Cooling rates would be expected to be the same since the same tubes and other materials are in place which would reasonably result in the same heat transfer rate.

It is noted that certain claims have been rejected above directed to means for controlling the heating and cooling as this means is clearly automated into the Perkin Elmer thermocycler regarding temperatures and times. It is also noted that fluorescence is seen in the Higuchi et al. tubes from all parts of the tubes including ends etc.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the real time monitoring of PCR in Higuchi et al. with the motivation to utilize the faster model 9600 thermocycler of Haff et al. to result in a reasonable expectation of success in practicing the instant invention.

Claims 13-20, 23-25, 28-31, 128-132, 135-137, 140-143, 156-160, and 168-170 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Haff et al. (P/N 5,720,923).

Haff et al. described PCR amplification in a computer controlled apparatus which allows for adjusting the reaction parameters as needed for sufficient amplification. An option for detection is described in column 26, lines 13-57, wherein the capillary tubes utilized in the apparatus are transparent enough to permit UV and visible light and are subject also to fluorescent type detection means. It is noted that several wavelengths of fluorescence is cited in column 26, lines 25-28, as also required in instant claim 33. The detection is preferred to be real time as set forth in column 8, lines 12-22, with one option depicted in Figure 30 where the light passes through the tubing at least twice. The reaction volumes can be 100 ul to about 1 milliliter as noted in column 7, lines 21-24, and column 10, lines 48-64, which are utilized to position the PCR sample throughout the thermocycling and may be made of glass or plastic. Various computer controlling descriptions such as using a CPU are scattered throughout the reference, for example, in column 9, lines 1-14. Various heating and cooling means are described including gas such as in the bridging paragraph between columns 9 and 10. In column 11, lines 17-26, the temperatures in the thermocycle are exemplified as 60 degrees C. for

annealing/extension and 95 degrees C. for denaturation. This gives a 35 degree C. temperature change during a thermocycle. In column 12, lines 26-37, the thermocycle time is stated as being as short as 8 seconds. Thus, a 35 degree C. temperature change must occur twice in 8 seconds which is approximately 35 degrees C. per 4 seconds or 8.75 degrees C. change per second. Another option is to arrange the sample tubes in a rotary device which is deemed a carousel as described in column 22, line 22, through column 32, line 10. The capillary tubes of Haff et al. are of various sizes with one size being 1-2 mm inside diameter as noted in column 8, lines 23-26. Thus volume to surface area ratio of such a capillary is  $\pi r^2 l / 2\pi r l = r/2$ . Thus a 1 mm capillary will have a 0.5 mm volume to surface area ration and a 2 mm capillary will have a 1 mm ratio of volume to surface area. Thus, the less than 1 mm volume to surface area ratio sample vessels of the instant claims are also described as options within Haff et al. These options thus are suggested and motivated as options which result in the practice of the instant invention.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the suggested options in Haff et al. to result in the practice of the above listed instant claims.

Claims 13-25, 28-31, 33-35, 55-59, 128-137, 140-143, 145, 146, 156-160, and 163-170 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Haff et al. (P/N 5,720,923); taken in view of Schregenberger (P/N 4,326,342).

The descriptions of the basic instant invention is described above in Haff et al. but without detailing the temperature control oven embodiments therein. Thus usage of such a oven for hot and cold temperature control is motivated in the bridging paragraph between columns 9 and 10 of Haff et al.

Schregenberger describes a generic multizone oven which would be required for the hot and cold temperatures such as required in a PCR reaction oven. This oven includes many fans which produced a forced air or gas flow arrangement for temperature control as noted in the Figures as well as the abstract and the reference as a whole.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize fans for air or gas forced ovens in order to obtain multizone temperature control as needed and suggested in Haff et al. and supplied for such ovens in Schregenberger thus resulting in the practice of the instant invention.

Claims 13-35, 55-59, 79-82, 87-90, 118-125, 128-148, 151, 156-160, and 163-170 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Haff et al. (P/N 5,720,923); taken in view

of Schregenberger (P/N 4,326,342), taken further in view of Jordan (P/N 4,325,910).

The combination of Haff et al. in view of Schregenberger has been summarized above but lacks the manner of detection of emitted radiation signal from fluorescence that passes or impinges through the end of the sample container as in instant claims 26 and 27, or, alternatively, illuminates and detects such a signal via a light path which is substantially parallel to a wall of a second or long dimension of the sample container as in instant claim 79, last 6 lines. Haff et al. in column 26, lines 13-57, describes detection of fluorescent signals including multi-wavelength detection such as utilizing a polychromator in line 26. Haff et al., however, also suggests and motivates the usage of other detection systems in column 26, line 23, without specifying which ones, but rather generically suggests others via the generic phrase "other detection systems". It is noted that different emission spectra signals are indicated in column 26, lines 25-28, to distinguish different reaction mixture components.

Jordan is a disclosure of various detection setups for light signals from sample analysis as summarized in the abstract of the reference. The device of Jordan is also noted as being depicted in various Figures as being a rotary or carousel device. Figure 5 specifically shows light paths which are substantially parallel

to the long dimension of the sample container as does Figure 9 in Jordan as well as passing through ends of the sample container. The general type of device and analysis is in the same general subject area as Haff et al. as noted in Jordan in column 1, lines 15-68. Figure 5 is discussed in Jordan in column 14, line 38, through column 15, line 51, wherein column 14, lines 38-43, specifically include fluorometric measurements, which are deemed to be of the fluorescence type as in Haff et al. The cuvette of Figure 5 is discussed in said column 14-15 via its light paths as shown in Figure 5 which supports this aspect of the rejection regarding light paths which are substantially parallel to the long dimension, or second dimension as instantly claimed. Also, Figure 9 is discussed in column 18, line 52, through column 19, line 33, as also measuring light beams which pass parallel to the long dimension of the cuvette with sample therein.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of Haff et al. in view of Schregenberger as discussed above which suggests and motivates multi-signal fluorescent measurements as in the art, including in carousels, of which Jordan is such an art reference including carousel measurements, thus resulting in the practice of the instant invention.

Claims 13-35, 55-59, 79-82, 87-92, 118-160, and 163-170 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Haff et al. (P/N 5,720,923); taken in view of Schregenberger (P/N 4,326,342), taken further in view of Jordan (P/N 4,325,910), taken further in view of Schembri (P/N 5,472,603).

The combination of Haff et al., Schregenberger, and Jordan have been summarized above but lacks the practice of utilizing a biasing force, optionally from carousel rotation to move sample fluids in the system and prevent undesired back movement.

Schembri describes an analytical rotor with chambers as well as the prevention of flow unless rotational speed is increased in the abstract. The rotor embodiments of Schembri are motivated and suggested for usage as desired in a wide variety of biological material analyses as noted in column 1, lines 15-48. The rotor use for reagent mixing etc. is suggested in column 1, line 49, through column 2, line 10. Several prior art citations are noted in Schembri in column 2, line 11, through column 3, line 7, as supporting the well known art based usage of centrifugal/centripetal force for sample or reagent movement during various analyses. The siphoning and centrifugal force usage in the rotor of Schembri for moving fluids is detailed in column 4, line 16, through column 11, line 52. Fluorescence measurements are included in the analyses as noted in column 9, lines 6-10, as also utilized in the other references in support

of this rejection. Fluids are introduced into the device and their flow controlled throughout analyses as described, for example, in column 9, line 51, through column 10, line 67. Each step in the fluid movement is controlled by capillarity or centrifugal force via rotor rotation which would include prevention of backflow into receiving ports or other chambers.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to control fluid or reagent flow as in Schembri as motivated and suggested therein for biological material analyses as performed in the combination of Haff et al., Schregenberger, and Jordan thus resulting in the practice of the instant invention.

Claims 161, 162, 171, and 172 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tina Plunkett, whose telephone number is (703)305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

September 27, 2002

*Ardin H. Marschel*  
ARDIN H. MARSCHEL  
PRIMARY EXAMINER